a few nanoseconds and retain the same orientation obtained from the all-atom membrane models. The interaction between st-lipid and GLA domain took ~20ns to achieve the same extent as seen in the all-atom models (Structure (2008) 16, 72). This membrane insertion process is also spontaneous, eliminating need of artificial manipulation such as pulling the proteins toward the membrane as performed in steered MD. Repeated short MD simulations using the membrane-mimetic model would form an ideal tool for investigating membrane insertion of proteins to achieve the initial state-independent results with good statistics.

3463-Pos Board B568

The Fukutin Transmembrane Domain: Capturing the Complexity of the Golgi Apparatus Membrane via Multiscale MD Simulations

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The membrane of the Golgi apparatus is a complex mixture of lipids and proteins. In the present work we describe multiscale molecular dynamics simulations of transmembrane protein domains in model membranes that represent the in vivo Golgi environment. The transmembrane domain of glycosyltransferases is required for their correct sorting within the Golgi apparatus. The hydrophobic thickness and oligomerization state of the transmembrane domains have been proposed to mediate this sorting. Fukutin, is a putative Golgi glycosyltransferase implicated in muscular dystrophy.

We employ atomistic and coarse-grained molecular dynamics simulations to investigate the stability and membrane interactions of the fukutin transmembrane domain, using various models of the membrane. Our atomistic simulations reveal that the fukutin transmembrane domain can exist as a stable α helix irrespective of the headgroup charge, fatty acid saturation or hydrophobic thickness of the lipid bilayer. Coarse-grained simulations reveal that the tilt angle of the fukutin transmembrane domain is highly variable and dependent upon its local environment; both the hydrophobic thickness and the headgroup charge of the lipid bilayer can alter the tilt angle of the protein. Lastly, we study the dynamics of the fukutin transmembrane domain in a mixed lipid bilayer whose composition closely mimics the complex lipid headgroup composition of the Golgi apparatus.

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High-Resolution, Solvent-Free Coarse-Grained Model for Protein-Lipid Interactions

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Many biophysical processes involving the interaction of proteins with membranes operate at time- and length-scales that are currently unattainable by all-atom computer simulations. To cope with this difficulty, increasingly more accurate and sophisticated coarse-grained models—both for proteins and lipids—are currently being developed.

In this work, we combine two high-resolution, solvent-free coarse-grained models for proteins and lipids. Proteins are modeled by four beads per amino acid, providing enough backbone resolution to avoid explicit secondary structure bias towards the native state [Bereau and Deserno, J. Chem. Phys. 130, 235106 (2009)], while the lipid model was systematically tuned to reproduce the structural and mechanical properties of phosphocholine (PC) bilayers [Wang and Deserno, J. Phys. Chem. B 114, 11207 (2010); New J. Phys. 12, 095004 (2010)]. The transferrability of the two models across amino acid sequences and lipid species permits the investigation of a wide variety of scenarios, while the absence of explicit solvent allows for studies of large-scale phenomena.

The two models were cross-parametrized to reproduce atomistic potential of mean force curves for the insertion of amino acids across the bilayer. We will illustrate different features of the model by simulating a small peptide which exhibits different stable folds in and out of the bilayer. Similarities and differences with the popular MARTINI force field will be discussed.

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The Role of Domains and Proteins in the Function of Lung Surfactant

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Lung surfactant forms a thin film at the gas exchange interface in alveoli. The film reduces the surface tension which is necessary for breathing. The film consists of a monolayer at the air/water interface connected with bilayer reservoirs in water. Lung surfactant is composed of a mixture of saturated and unsaturated, zwitterionic and anionic lipids; surfactant proteins B (SP-B) and C are associated with the interface. Surfactant proteins facilitate adsorption of lipids to the interface likely via stalk-like intermediates. The proteins are also believed to induce monolayer collapse by creating nucleation sites/fluidizing effect. Lipid components in monolayer segregate into domains of coexisting phases, which is suggested to increase monolayer stability. However, the exact mechanisms of these effects are still not fully understood.

We study the role of phase coexistence and proteins in the function of lung surfactant. Molecular dynamics simulations with the coarse-grained model MARTINI are employed. We simulate mixtures of saturated and unsaturated phosphatidylcholine and phosphatidylglycerol lipids, cholesterol and SP-B proteins. The model of SP-B is built based on homology with the saposin family and was shown previously to mediate early stages of vesicle fusion [S Baoukina, DP Tieleman, Biophys J, 2010]. We reproduce phase separation into liquid-expanded (LE) and liquid-condensed (LC) or liquid ordered (Lo) phases in monolayers. SP-B partitions into the LE phase and prevents formation of the LC phase at conditions close to the phase transition. The protein also enhances lipid de-mixing. SP-B dimers induce bilayer folds in monolayers at positive surface tensions below the equilibrium spreading value. Monolayer collapse is initiated from the LE phase, and the composition of bilayer folds differs from the monolayer. SP-B anchors monolayers and bilayers and promotes lipid transfer.

3466-Pos Board B571

Multi-Scale Molecular Dynamics Simulations of a Membrane Protein Stabilizing Polymer

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Amphipathic polymers have been developed as an alternative to detergents for the stabilization of membrane proteins during structural characterization. These polymers have been demonstrated to provide a less dissociative environment than detergents, and are thus able to sustain the native, oligomeric state of membrane proteins. The most successful polymer, A8-35, consists of a hydrophilic polyacrylate backbone with hydrophobic octylamine groups covalently attached. In order to better understand the mechanism by which these A8-35 polymers bind and stabilize membrane proteins, we present two sets of simulations. First, we present a series of all-atom molecular dynamics (AAMD) simulations of the amphipol particle in solution. Experimental studies have shown that the polymer forms cohesive particles consisting of four chains. While our AAMD simulations result in cohesive and stable particles over a 45 ns simulation, and whose structure is in agreement with small angle neutron scattering, the equilibration of the particle structure is limited in AAMD. Therefore, we present a second series of simulations using coarse-grained molecular dynamics (CGMD). This includes parameterization of the bonded and non-bonded terms in the Martini force field, and comparison of the particles formed by microsecond-scale CGMD with the particles formed by AAMD. Finally, we present initial simulations of the amphipol polymer interaction with lipid bilayers and membrane proteins.

3467-Pos Board B572

Molecular Simulation Study of Prion Peptide Self-Aggregation in the Presence of Lipid Membranes

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Neurodegenerative pathologies such as Alzheimer's disease affect millions of people worldwide and are a major cause of morbidity and mortality. One such cause of dementia, Creutzfeld-Jakob disease, is thought to be caused by the human prion protein PrP. Interactions with membranes have been shown to affect the behaviour of amyloid-forming peptides, including prion peptides, and have been implicated in their toxicity. To gain insight into the molecular basis of these effects, we use atomistic molecular dynamics simulations in explicit solvent to examine the interaction of several blocked PrP and yeast-prion protein fragments with zwitterionic and anionic lipid bilayers. All four oligopeptide sequences are studied at different concentrations, successively in the presence of phosphatidylcholine (POPC, zwitterionic) and phosphatidylserine (POPS, anionic) bilayers, for a total of 0.12 ms of simulation time. Peptide-lipid interactions are characterized and the effect of peptide binding to the lipid bilayers on the conformational ensemble and self-aggregation properties of the peptides is analyzed. Possible implications of these findings to prion peptide toxicity are discussed.